MAXIMO VENTO PODCAST TRANSCRIPT

Geoff Marsh
Hello. Thanks for downloading another Pediapod. This episode, along with a few more to come, involves a conversation with a senior investigator who has had a large and lasting effect in the world of pediatric research. The Early Career Investigator episodes will still be coming once a month, but hopefully this will add a bit of variety to the Pediapod feed and shine a light on some of the pioneers who have helped shape the face of modern Pediatrics. This episode features Max Vento.

Maximo Vento
My name is Max Vento. I am a neonatologist based in Valencia, Spain. I work in the University Hospital La Fe. I am the director of the Neonatal Research Group that works in the Health Research Institute in the same hospital. We are a group that is formed of people coming from different backgrounds such as medical and nursing backgrounds but we have also chemists, we have biologists, so all together we have a complex, multidisciplinary group that are devoted to research, especially in the field of fetal to neonatal transition

Geoff Marsh
Well you sound like a busy man so we appreciate you giving up your time to come on the podcast. Why don't you start by taking us back and telling us a little bit about how you got to be where you are today?

Maximo Vento
Well, I have liked biology since I was very young. And my doubt has always been whether to go into biology or medicine. My father was an anesthesiologist and my mother was a pediatrician and they had interesting conversations at the dinner table about the difficult cases they have experienced in their working days. So finally I decided to go into medical school. When I was finishing my medical studies, I went to do my practice in pediatrics. And then I met Professor Manuel Moya and he introduced me both into experimental research and into clinical research, especially in the field of neonatology. I developed a rat model with him that was about the influence of calcium in rat offspring that have been submitted to different experimental conditions and this experiment formed the backbone of my PhD degree.

Geoff Marsh
Was that a real turning point for you, a sort of light bulb moment that maybe a future of research lay ahead of you?

Maximo Vento
Yeah, because I am talking about the years 1972 to 74 approximately. Experimental research done by doctors in Spain was very seldom done. So most of the doctors were devoted to doing

clinical trials and to trying new drugs and things like that. But to go into the lab and have an animal model, and in my case, I put forward the use of a new method of determination of minerals- it was atomic absorption spectrometry which was for the first time used in our hospital. It all gave me the sensation that I had finally been able to combine my old dreams of being a biologist with my new dreams of being a doctor. And this was a great pleasure for me and a source of very nice intellectual experiences.

Geoff Marsh
It's wonderful that you managed to combine the medicine and the research in one pursuit. Where did you go from there?

Maximo Vento
Yeah, well, I pursued different research questions and I was lucky to meet professor Ola Didrik Saugstad, who worked at the University of Oslo. And he was the feature lecture at the National Congress and he spoke about free radical disease of the newborn infants. I had done some experiments with Professor Viña studying the fetal-to-neonatal transition and how this affected oxidative stress metabolism.

Geoff Marsh
Was that lecture really the birth of our understanding of hyperoxia?

Maximo Vento
Yeah, I think that what professor Saugstad did was to combine findings from different conditions that happened in the brain, in the lung or other organs, under a common and unifying theory. The unifying theory was the free radical disease of the newborn. And since I had been working in the lab and I had been experimenting with markers of oxidative stress, I understood perfectly what he meant. And then from then on, we translated our findings into the practical world and we started to do clinical trials. What we saw was that when a tissue was subjected to hypoxia, as happens, for example, in asphyxiated babies, you accumulate substances that derive from ATP, the molecule that gives us the energy. When you don't receive oxygen, then you degrade ATP to basic substances that are called xanthines, especially hypoxanthine. The peculiarity of this substance is that when you reoxygenate during resuscitation and give a burst of oxygen to this tissue, this tissue is going to generate a burst of oxygen free radicals that are going to expand the initial lesion and make the damage that was caused initially expanded and increased by the action of supplemental oxygen.

Geoff Marsh
So then did it become clear to you that pure oxygen was maybe more dangerous than it was helpful?

Maximo Vento
Well, these studies were done mainly by Dr. Saugstad in his newborn piglet model and also in rat models. What he saw is that using lower concentrations of oxygen upon resuscitation of

these asphyxiated animals, reduced the damage and allowed them to recover. So what we did is we organized a meeting in Valencia with different people coming from different countries and we launched several trials that went from the first trial planned by Dr. Saugstad in 1993 in India, that was a feasibility trial, and then he performed what was called the Resair 1 trial. Both these trials showed that it was feasible to resuscitate babies in the delivery room with room air. And then he launched a multicenter trial in which we participated and this was called the Resair 2 Trial. In this study there was an increased number of babies and they showed again that not only was it feasible to resuscitate with air but we got the babies recovered earlier, started to breathe earlier to cry earlier, and there were good clinical results. There were some problems with the experimental design, for example, it wasn't blinded. Secondly, it didn't have a biochemical background, it was just a clinical study. So what I did is that I performed three or four randomized clinical trials in which I blinded the oxygen source for the people resuscitating in the delivery room. So for the first time in neonatology we had a blinded trial in the delivery room. The second thing I did is that I took blood before and after resuscitation and analyzed different oxidative stress markers and I proved that resuscitation with high oxygen content caused an intense and very damaging oxidative stress that expanded the initial lesions to more severe lesions. So we were causing more damage, amplifying the damage during resuscitation. We included a follow up, a biochemical follow up in these babies that showed that sometimes, oxidative stress did not finish after the intervention, but it could get prolonged in time having other consequences, such as prolonged inflammation and genetic alterations.

Geoff Marsh
What were the long lasting impacts of that research?

Maximo Vento
When we did a meta analysis in 2008, the result was highly significant in favor of room air. So room air resuscitated babies died less and there was a tendency to reduce brain damage in these babies. This was a striking finding that convinced the International Liaison Committee on Resuscitation in 2010, for the first time to write a paragraph in which it says it was feasible and also advisable to use room air as the first option to resuscitate asphyctic babies. And in case that room air was not enough done, the oxygen blender should be increased to provide enough oxygen to stabilize these babies.

Geoff Marsh
Can you explain how that ended up being beneficial for doctors in low-middle income countries?

Maximo Vento
Well imagine that until then babies born in low-middle income countries, many of them in the rural areas in small villages where oxygen was not present, where they didn't have any access to oxygen. So if they didn't start breathing immediately after birth they were considered stillbirths and they weren't abandoned to die. With our findings, when they were incorporated by neonatologists all over the world, especially non-governmental organizations such as Médecins Sans Frontières, or Helping Babies Breathe, when they started to employ a very basic positive

pressure resuscitation devices, they could resuscitate a baby or at least try to enhance respiration in these babies in any place without having the need for having an oxygen bottle and all the devices that are needed to provide oxygen. So we recently published a paper with Dr. Wally Carlo from Birmingham, Alabama, in which it was shown that hundreds of thousands of babies are being saved every year because they are able to be resuscitated with room air. And I think that Dr. Saugstad deserves credit for that.

Geoff Marsh
And you must feel some sense of pride to have been a part of that?

Maximo Vento
Well, yeah, I am very proud and very happy about it but as we always say in science, science is characterized by disbelief. So we always think that there is something that we can do even better.

Geoff Marsh
In terms of improving things, what do you see as some of the big issues confronting neonatology today and in the future?

Maximo Vento
Geoff, you mentioned something important- the question regarding low-middle income countries. If you review the most important journals in neonatology - or in any type of medicine but I am centering my intervention in neonatology - there are highly sophisticated interventions in highly sophisticated settings, with very experienced groups and what I call the chain of interventions which starts in the control of pregnancy, they attendants to delivery, the resuscitation and post-resuscitation, everything is perfect in the chain. However, if you apply something that you have discovered, a new protocol, in a low-middle income country, the chain is not completely developed. You may have a lot of women who haven't had good control of their pregnancy, perhaps the delivery room doesn't have the means of resuscitating or the hospital doesn't have the monitoring systems, et cetera. So we should design our studies in close cooperation with obstetricians, nurses, and neonatologists from these countries and our studies should take into consideration the reality of these countries. And then we could do the correct interventions to save the lives of more than 130 million babies that are born in these countries compared to 10 or 15 that are born in our countries.

Geoff Marsh
Yeah, the basic science is the same all over the world but the applicability of those findings in different contexts requires input from those contexts.

Maximo Vento
Exactly. Yeah.

Geoff Marsh

And is that happening? Is that something people are talking about?

Maximo Vento
Well, there is an example. When you compare our trials that Dr. Saugstad initially performed in India, we had all the setup for the experiments thinking of what the reality in India was at that time. Now, the HELIX trial has been recently published and they have used hypothermia. Hypothermia in level three hospitals in India. These hospitals were exactly the same as if they were in England. They had all the means of taking care of babies, they had neonatologists, all the set up in an the NICU was similar. However, hypothermia in India caused more deaths than nonintervention which didn't happen in any of the high income countries. What was the problem? The problem was that these babies arrived to hospital and many of them were already so sick that hypothermia was a second hit that worsened their condition. So what we should do is when we are going to translate our findings or our new means of treating illnesses, we have to adapt our means to these countries. I think this would be very interesting and I think that is the future of global thinking regarding medicine.

Geoff Marsh
What lessons did you learn from your position that you sit in between basic research and the clinic, what have you learned about how to do research and how to make it useful?

Maximo Vento
The first thing is that I don't think that everybody has a mind for research, just like not everybody can be a good soccer player, you know. To be a researcher you have to have a great curiosity, you have to be asking yourself questions every day. This is the real engine that moves science. And the second point would be that you need to look for a mentor, someone in your surroundings or even in another country if you are able to visit, and establish professional relationships with a strong group with a good mentor and be able to start seriously to do research. Research these days is extremely expensive. Even in my country, Spain, which I consider to be in the top 20 countries in the world, research is more focused on adult medicine. There is little money for neonates. Neonates always have the problem that they represent a very small part of the society and they don't vote. So neonates are always abandoned. So you have to make extra effort in order to have a link with a good research group so that these people can help you to design your projects to get funding and to be successful. And then admit that if you're a doctor, you have to see patients and then you have to add additional time to reading papers, to writing papers to do animal experiments. This is very tough because it takes a lot of time, from your private life, the time with your family, the weekends, vacation, etc. And not everybody is ready to accept that situation.

Geoff Marsh
You mentioned mentors. It sounds like you've been very fortuitous when it comes to senior researchers who really steered you along along your early career path. Are you giving back? Are you mentoring, yourself and what advice do you have for the next generation of pediatricians?

Maximo Vento
Well, luckily I have very close contact with young researchers in my group but also in groups from other countries. I think that young people now are much better prepared, at least in Spain, than we were in the 70s. But the paradigm has changed. When I started I did everything myself. Now, in order to do high-tech research, or to answer difficult questions you need to have people with a multidisciplinary background in your group. So if you're a neonatologist, you have to be ready to speak with biologists, with analytical chemists, with bioinformaticians, people who can look at your problem from different perspectives and together, design a project and give an answer to the problem. And I think that's the reality these days. I think our young people are very prepared, and the people from my generation are also ready to give them all our support, because science cannot stop.